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Review of current evidence available for guiding optimal Enoxaparin prophylactic dosing strategies in obese patients—Actual Weight-based vs Fixed

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ABSTRACT

Background: The current debate over the optimal Enoxaparin prophylactic dosing strategies in obese patients centre around whether it should be based on the actual weight of the patient (i.e. weight-based), or at an artificially fixed amount, as it is the case in Australia (40 mg daily). The vast majority of the evidence available today is laboratory-based, measuring serum Antifactor-X_a activities as a marker for physiological response.
Aim: The aim of the parent study is to compare the clinical outcomes for obese patients who received fixed doses of enoxaparin compared to those who received weight-based doses within the licensed dosage recommendations. This review was conducted to examine whether a gap in knowledge exists in relation to dosing obese patients with enoxaparin as VTE prophylaxis after hospital admission to aid in development of the parent study concept.
Method: Databases such as Medline, EBSCOhost, ProQuest were interrogated using combinations of words such as "enoxaparin", AND "dosing strategy", AND "obese/obesity" AND "prophylaxis". Only eleven out of 14 primary studies which were considered to be sufficiently similar in methodology and anticipated outcomes were reviewed and analysed.
Results: Pooled data from the eleven studies suggested that weight-based or higher-than-fixed dosing had a 36.2% higher success rate than fixed dosing, and was more likely to achieve the desired serum Anti-X_a activity levels (52.2% and 16% respectively). The rate of failure to achieve this is significantly lower in the weight-based groups (13.3%) than in fixed-dose groups (18.5%). These eleven studies reviewed included 601 patients in total.
Conclusion: There is insufficient evidence to support or negate the current enoxaparin health outcomes in obese and very obese patients due to the lack of post-discharge follow-up from hospitals. Further research is required to compare long-term outcomes after fixed and weight-based dosing of enoxaparin. The optimal dose of enoxaparin per kilogram of body weight for prophylaxis remains to be determined.

1. Introduction

Enoxaparin is widely used for number of cardiovascular indications. It is a semi-synthetic Low Molecular Weight Heparin (LMWH)

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of approximately 4500 Da in molecular weight. LMWH is an indirect thrombin inhibitor, initiated through forming a complex with anti-thrombin, mediated through the pentasaccharide sequence located along the LMWH chain causing a conformational change to the anti-thrombin. This complex then acts as a catalyst to accelerate the inactivation of coagulation Factor-X_a leading to amplified anti-thrombin actions, by 1000-fold, with thrombin and Factor-X_a. (Marmur et al., 2009; MIMS Australia, 2013). LMWH promotes the release of Tissue Factors Pathway Inhibitor (TFPI) from the vascular endothelium and fibrinolysis. To a lesser extent than unfractionated heparins, LMWHs reduce the level of the von Willebrand factor (vWf), inhibit the pro-coagulation effect of leukocytes and inhibit monocyte adhesion. One of enoxaparin's key indications in a hospital setting is its use as prophylaxis against venous thromboembolism (VTE), which includes both pulmonary embolism (PE) and deep-vein thrombosis (DVT). Its fast onset of action provides protection against VTE events, as well as a superior profile in both efficacy and safety compared to warfarin, make it the 'drug of choice' for many clinicians.

Due to its nature as a LMWH, it is also referred to as 'fractionated heparin'. Since it is cleaved and stabilised ex-vivo during the manufacturing process, before it is administered to the human body, it exhibits a more stable and predictable pharmacokinetic profile (MIMS Australia, 2013), resulting in a superior choice to unfractionated heparins for medium- to long-term prophylaxis against VTE. This is particularly important in a community setting or post-discharge from hospital, where less direct medical care and monitoring are available to patients. Therefore, due to its comparatively fewer incidences of haemorrhagic events and thus a safer choice in prophylactic therapy, it is now a clinicians' choice for prophylaxis against VTE over its unfractionated counterpart (Hyers et al., 2001).

2. Materials and method

The literature search was conducted using the Primo Search® search engine to access databases such as Medline, EBSCOhost, ProQuest. The search was conducted using the terms, or combination of those terms, including 'enoxaparin', 'dosing', 'weight', 'obesity' and 'prophylaxis', plus any one or all of the following terms: 'DVT (Deep Vein Thrombosis)', 'PE (Pulmonary Embolism)' or 'venous thromboembolism'.

The following criteria were developed to select the publications included in this review. For a study to be included, it had to be:

- Original research;
- Peer reviewed;
- Published;
- Patient-control design;
- Evidence of structured statistical analysis performed, and weight was one of the study variables.

The research parameters must also include weight at least as part of its consideration, if not one of the primary inclusion criteria. Both retrospective and prospective studies were included in this review.

These papers were then analysed for similarities and differences between study aims, target patient group(s), and methodology. Studies that were deemed to be sufficiently similar were included in this review.

3. Results

A total of 14 peer-reviewed publications, meta-analyses and guidelines were found to be original publications and relevant to this topic, two studies were excluded as the method and markers were different to that of the other twelve studies (Hamad and Choban, 2005; Richard et al., 2013). The former was excluded on the grounds that they used monitoring techniques and markers that are non-haematological; the latter was targeting a different demographic (paediatric). Twelve publications measured the Anti-Factor X_a (anti-X_a) activity as a clinical endpoint or surrogate marker for the apparent efficacy of enoxaparin in test subjects, with only one publication that took patients' post-discharge monitoring into its primary consideration (Woo and Kim, 2013). One study used, in conjunction with anti-X_a levels, Thrombin-Antithrombin concentration levels as a marker (Desjardins et al., 2004). It enrolled five patients of which only four agreed to be followed up after discharge from the hospital. This sample is small and constitutes only 8.6% of total patients who received enoxaparin prophylaxis, which means that the findings may not be consistently reproducible and accordingly it was excluded, leaving only eleven studies that can be directly compared.

When Anti-X_a activity levels were used as the surrogate marker for enoxaparin prophylaxis (11 studies out of reviewed 14), dosing was either 'fixed' dose at 40 mg daily and was considered to be sufficient, or higher dose(s) weight-based dose, usually 0.5 mg/kg once daily, or in divided doses twice daily. These two groups included some head-to-head comparison studies, whilst others have taken the null hypothesis of 'Weight-based dosing is necessary for obese patients'. The latter of those tend to select an entire sample of patients who are overweight and give them fixed dosing and to compare them to those given weight-based dosing; whilst the former give both the 'normal' weight and 'obese' patient groups the same fixed dose, and compare the resultant the Anti-X_a activity in each group.

It was also worth noting that each study's target Anti-X_a levels might vary, ranging from <0.1–0.5 IU/ml (Kopelman et al., 2013), to 0.18–0.44 being 'therapeutic' according to *Simone* et al. The serum levels in most of these studies were taken as post-dose peak levels, and repeated if multiple doses were administered. It was beyond the scope of this review to consider each single range of those studies individually. Therefore, 'success' was defined as the ability to reach the subjective target of each of these studies' pre-determined range(s).

Whilst some studies such as Rowan et al. (2008) explicitly state the mean BMI of the majority of the surgical patient cohort (e.g. 48.5 kg/m^2 in 82% of subjects), others have only included mean weight of its participants receiving trauma-related surgery (103.3 kg ± 20.8 kg), with no clear indication of BMI or even height (Kopelman et al., 2013). This appears to indicate a major gap in the availability of studies with consistent patient demographics or record of physical attributes.

4. Discussion

There appears to be insufficient evidence to guide clinical practice surrounding the dose selection of enoxaparin when administered to obese or morbidly-obese adult (Australian Bureau of Statistics, 2011) patients for prophylaxis against venous thromboembolism (both Pulmonary Embolism and Deep Vein Thrombosis). The controversy of enoxaparin prophylaxis dosing largely falls under two groups: those advocating for a fixed dosing (Richard et al., 2013; Hiscock et al., 2013; Xu et al., 2012) and those advocating for a weight-based dosing (Kopelman et al., 2013; Bickford et al., 2013; Rondina et al., 2010). The former group express an opinion that the dose, regardless of the actual patient weight, should be limited to or capped 40 mg daily. The latter believes that there should be no such artificial cap, and patients should be dosed according to their actual weight as per the current treat-